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Study looks at stem cells for answers to how a type of autism develops

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The lab of Yongchao Ma, Ph.D., from Stanley Manne Children's Research Institute at Ann & Robert H. Lurie Children's Hospital of Chicago, discovered how the genetic defect in fragile X syndrome—a type of autism—delays production of neurons (nerve cells) at a critical time in the embryo's brain development. In a study published in *Cell Reports*, Dr. Ma and colleagues describe a previously unknown regulatory mechanism controlling how stem cells differentiate into neurons. They identified early disruptions in this process in fragile X syndrome, the most common inherited intellectual disability in children.

"During embryonic brain development, the right neurons have to be produced at the right time and in the right numbers," says Dr. Ma, senior author and researcher at Lurie Children's, as well as Associate Professor of Pediatrics, Neurology and Physiology at Northwestern University Feinberg School of Medicine. "We focused on what happens in the stem cells that leads to slower production of neurons that are responsible for brain functions including learning and memory. Our discoveries shed light on the earliest stages of disease development and offer novel targets for potential treatments."

Other studies in fragile X development have focused on the interactions between mature neurons. Dr. Ma's study is the first to offer a new understanding of the disease at a stem cell level.

Fragile X syndrome occurs in approximately 1 in 4,000 males and 1 in 8,000 females. It is caused by mutation in the gene called FMR1 that

encodes a protein called FMRP. The genetic defect leads to reduced FMRP protein. Previously the function of FMRP protein during early brain development was not known.

Dr. Ma and colleagues discovered that within a stem cell, the FMRP protein plays a key role as a "reader" of a chemical tag (called m6A) on the RNA. This tag carries instructions on how to process the RNA. By reading these instructions, FMRP protein exports the RNAs from the nucleus to the cytoplasm of cells where the m6A-tagged RNAs will become proteins that control stem cell differentiation into neurons.

"We show how the reduced amount of FMRP protein in neural stem cell results in decreased nuclear export of m6A-tagged RNAs and ultimately, slower production of the neurons that are essential for healthy brain development," says first author Brittany Edens, graduate student in the Northwestern University Interdepartmental Neuroscience Program who works in Dr. Ma's lab. "Our findings also expand understanding of how the flow of genetic information form DNA to RNA to protein is regulated, which is a central question in biology."

"Currently we are exploring how to stimulate FMRP protein activity in the stem cell, in order to correct the timing of neuron production and ensure that the correct amount and types of neurons are available to the developing brain," says Dr. Ma. "There may be potential for gene therapy for fragile X syndrome."

Provided by Ann & Robert H. Lurie Children's Hospital of Chicago